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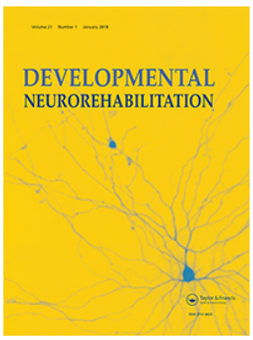

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BRIEF REPORT

Early development in Rett syndrome – the benefits and difficulties of a birth cohort approach

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ABSTRACT

Purposes: Typically, early (pre-diagnostic) development in individuals later diagnosed with Rett syndrome (RTT) has been investigated retrospectively using parent reports, medical records and analysis of home videos. In recent years, prospective research designs have been increasingly applied to the investigation of early development in individuals with late phenotypical onset disorders, for example, autism spectrum disorder. *Methods:* In this study, data collected by the Danish National Birth Cohort lent itself to prospective exploration of the early development of RTT, in particular early motor-, speech-language, and socio-communicative behaviors, mood, and sleep. *Results and Conclusions:* Despite limitations, this quasi prospective methodology proved promising. In order to add substantially to the body of knowledge, however, specific questions relating to peculiarites in early development could usefully be added to future cohort studies. As this involves considerable work, it may be more realistic to consider a set of indicators which point to a number of developmental disorders rather than to one.

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Introduction

Mutations in the X-linked methyl-CpG-binding protein 2 gene (*MECP2*) are the main cause of Rett syndrome (RTT; OMIM #312750), a genetic disorder affecting neurodevelopment, with a prevalence of approximately 1 in 10,000 live female births.[1–4] The natural history of this disorder follows a four-stage trajectory including a period of regression with subsequent recovery or stabilization.[3,5] Hagberg[5] reported on 35 females characterized inter alia by loss of verbal communicative abilities and purposeful hand use with simultaneously occurring hand stereotypies (hand wringing, washing character). He published his findings under the eponym of the author who first described this symptom-complex some 50 years ago, the Austrian neuropediatrician Andreas Rett.[6] Since then, consensus clinical criteria have been developed and constantly modified according to the scientific and clinical advances in the study of RTT.[4,7] The main mutation responsible for this clinical condition was discovered more than 30 years after its first description,[1] and a classification system differentiating between typical RTT and atypical RTT (or RTT variants, such as preserved speech variant, early seizure variant, congenital variant) has been established.[4,8] In recent years, numerous studies on the aetiology of the disorder, the epidemiology, the treatment, and potential advances in facilitating earlier diagnosis have been conducted. Notwithstanding growing evidence about early neurobehavioral alterations in infants and toddlers with RTT prior to the onset of regression and diagnosis,[9–20] there is still a widespread believe among many clinicians and scientists that early development is normal before obvious regression.

The body of evidence for atypical early development in RTT and the attempts to define behavioral biomarkers or neurofunctional markers of maldevelopment in motor-, speech-language, and socio-communicative domains stem almost exclusively from retrospective data analyses. The two major approaches to outlining developmental trajectories prior to diagnosis of individuals with any type of late phenotypical onset disorders are based on (a) medical records and parental reports, or (b) analyses of home videos. Both approaches have contributed to our understanding of developmental characteristics of RTT, but they clearly have limitations.[21–26]

In recent years, prospective research designs have been increasingly applied to the investigation of early development in autism spectrum disorder (ASD) and even some rare diseases such as fragile X syndrome.[27–29] Prospective studies have without any doubt advantages over retrospective designs, that are influenced, e.g., by time lag, memory bias and forward telescoping effects, awareness of the diagnosis at the time of the interview, etc.,[21,22,30] yet is hard to apply in rare disorders without a family history. Other sources of prospective data include cohort and register studies. Register studies usually provide more general core data (medical, social, etc.)

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not intended to answer specific research questions. Access to the Danish National Birth Cohort (DNBC) allowed us to prospectively explore the early development of RTT. The aim of our study was to determine the added value of assessing medical and behavioral data from a cohort study to the understanding of the early phenotype of RTT. With the data available we specifically aimed to shed light on the following aspects of early development of RTT: (a) motor skills, (b) speech-language, (c) socio-communicative behaviors, and (d) mood and sleep.

Methods

The Danish National Birth Cohort

Between 1996 and 2002, a total of 101,042 pregnant women in Denmark consented to take part in a large nationwide longitudinal study.[31,32] They were interviewed by telephone during pregnancy and when the offspring was 6 and 18 months old. The interviews were designed to study the mother's lifestyle during pregnancy and the short- and long-term effects of this on the child, assessing a wide range of neurodevelopmental features in children but not to detect specific developmental disorders.[31] Details can be found at the DNBC homepage (DNBC 2013; www.dnbc.dk). At 12 weeks' gestation, information on the socio-economic status and educational background of the parents was collected. On occasions, an interview could not be conducted at the allotted time and had to be postponed. In such a case the participant was asked to provide the information pertinent to the originally-scheduled time (therefore quasi prospective design). If a participant was uncertain about an answer or had chosen not to answer a question, the answer was coded as missing.

The 6 and 18 month interviews consisted of more than 200 questions each. Data on motor, cognitive, speech-language and social parameters, as well as feeding, mood, sleeping, crying, hearing abilities, and vision were collected.[33,34]

Inclusion criteria

All citizens in Denmark are assigned a personal identification number from The Danish Civil Registration System at birth.[35] This personal-ID enables identification of Danish individuals across public registries. We included only participants living in Denmark through the entire period who had participated in the 12-week gestation interview and in at least one of the interviews at age 6 or 18 months. From the original cohort, 92% of the participants completed the first interview at 12 weeks' gestation. Seventy per cent participated at the 6 month interview and 66% at 18 months (DNBC, 2012). The study population comprised 76,322 children (39,046 girls).

Diagnosis of Rett syndrome

In Denmark, children suspected of having RTT are typically referred to a public pediatric department where evaluation and treatment is free of charge. In- and outpatient diagnoses assigned at public hospitals are registered using ICD-10 classifications in the Danish National Patient Register.[36] According to the Danish National Patient Register, six girls in the DNBC were identified with RTT (ICD-10 code F84.2).

Ethical considerations

The DNBC steering committee gave permission to use data from the cohort for this project. At the time of inclusion in the DNBC, the mothers gave consent to the usage of data for research and any resulting publications, and to the linkage with public registries in the future. The study was approved by the Danish National Board of Health and registered at the Danish Data Protection Agency. It should be noted that Statistics Denmark, the central authority on Danish statistics and the use of data (http://www.dst.dk), only allows extraction of data at group level where the individual cannot be identified. For any table, only cells containing at least three observations can be reported.

Results and discussion

The prevalence of RTT in this sub-cohort of DNBC is approximately 1 in 7,000 females. Four out of the six parents of individuals later diagnosed with RTT participated in the interview at 6 months post-delivery, and all took part in the 18 month interview. The mean age at the first interview was 6.4 months for the study cohort and 5.8 months for RTT; for the second interview, these were 19.2 months and 19.4 months respectively. The average age of RTT diagnosis was 2 years (range 1.6–2.3) (see Table 1).

At the time of the 6 month interview there appeared to be few differences in many of the developmental milestones that were assessed (see Table 2). One indicator of a possible delay in development that did emerge, however, was in relation to gross motor skills, with the reported mean age of sitting without support. In the cohort this was achieved at an average age of 6.5 months (SD = 1.25) whereas the mean age for those

Table 1. Characteristics of the DNBC study population (n = 76,322).

		Study cohort	Rett syndrome
Offspring's gender (%)	Male	37,276 (48.8)	0
	Female	39,046 (51.2)	6
Mean age at diagnosis, years (min/max)		N/A	2.0 (1.6/2.3)
Mean age at end of follow-up, years (min/max)		11.3 (8.6/13.9)	10.9 (9.0/13.2)
Mother's level of education[a] (%)	High	39,047 (53.4)	3
	Middle	27,748 (38.0)	3
	Low	6,324 (8.7)	0
Participated at the 6 month interview (%)		65,681 (86.1)	4
Mean age at the 6 month interview, months		6.4	5.8
Participated at the 18 month interview (%)		62,624 (82.1)	6
Mean age at the 18 month interview, months		19.2	19.4

[a]Mother's level of education was divided into three groups according to Lemcke et al.[34]

High = 4 years of education after high school; middle = skilled workers or with middle range training; low = unskilled or unemployed.

Table 2. Developmental aspects at 6 and 18 months; only descriptive data are presented due to the small sample size of individuals with Rett.

	Study cohort		Rett syndrome	
	Yes	No	Yes	No
	n (%)	*n* (%)	*n*	*n*
6 Month interview				
Motor behavior				
Supports head during traction	65,547 (99.8)	117 (0.2)	4	0
Sits upright on caregivers lap	59,069 (89.9)	6,475 (9.9)	4	0
Can crawl on stomach	35,069 (53.4)	30,493 (46.4)	4	0
Tries to grab things that are out of reach	64,579 (98.3)	1,005 (1.5)	4	0
Speech-language and socio-communication				
Orients to acoustic stimuli (sounds and voices)	65,312 (99.4)	273 (0.4)	4	0
Vocalizes spontaneously	64,718 (98.5)	870 (1.3)	4	0
Tries to make contact by reaching the caregiver	60,525 (92.1)	4,794 (7.3)	4	0
Has crying episode for more than 30 min	16,034 (24.4)	49,580 (75.5)	0	4
18 Month interview				
Motor behavior				
Walks without support at 18 months	61.704 (98.5)	817 (1.3)	0	6
Climbs stairs with support	59,580 (95.1)	2,603 (4.2)	0	6
Takes off socks and/or shoes	50,811 (81.1)	11,132 (17.8)	0	6
Fetches objects and brings them to others	60,527 (96.6)	1,179 (1.9)	0	6
Speech-language and socio-communication				
Has a productive vocabulary of >10 words	26,259 (41.9)	36,292 (58.0)	0	6
Produces word combinations	26,267 (41.9)	34,530 (55.1)	0	6
Remains at one task for at least 15 min	50,800 (81.1)	11,229 (17.9)	6	0
Mood and sleep				
Is a happy child	61,944 (98.9)	117 (0.2)	6	0
Active like kids the same age	61,619 (98.4)	789 (1.2)	3	3
Is restless in sleep	6,205 (9.9)	47,303 (75.5)	0	6

with RTT was 7 months (SD = 1.41). As the sample size of individuals with RTT was extremely small these results should be treated with caution. Yet, by the time of the 18 month interview significantly greater differences were apparent in several areas of gross motor ability, for example, none of the six females with RTT were able to walk without support whereas 98.7% of the cohort had achieved this milestone (mean age of walking was 12.6 months; SD = 1.8).

This pattern, of generally unremarkable differences in development at 6 months with more significant delays, especially in gross motor development, apparent by 18 months can be seen in other results from the 6 and 18 month interviews which are presented in Table 2. This shows findings for motor behavior, speech-language and socio-communication at the time of both interviews and, in addition, mood and sleep behaviors at 18 months of age. That said, it is also noticeable that although the six females with RTT appeared to show clear delays in their gross motor skills at 18 months, a number of tasks, particularly those in the speech-language and socio-communications domain, had not been achieved by a large proportion of either the cohort or those with RTT at this age. For example, a majority of the cohort, as well as the six individuals with RTT, did not have a vocabulary of more than 10 productive words nor did they combine words at 18 months of age (Table 2). With regard to mood and sleep, no apparent differences could be noted between children with RTT and the cohort.

Overall the results, inconspicuous behavior at 6 months with more obvious deviations by 18 months, were in line with previous findings and the reports by Neul and colleagues[3] in their recent large-scale natural history study on developmental delays in RTT (in a retrospective design), in which they state "Early developmental skills in RTT are acquired by many, but clear differences emerge in skills expected after 6 months of age" (Conclusions, p. 8). They go onto suggest that the commonly denoted appearance of normal early development in individuals with RTT "may be more apparent than real" (Abstract, p. 1). Over the last two-three decades the work of several groups of researchers and clinicians, including ourselves, has seen a steadily accumulating body of evidence which challenges the paradigm of normal early development.[9–11,13,15–18,20,37,38] Such studies have also begun to delineate different profiles in early development according to both RTT variant and mutation type.[2,3,39–43]

The majority of these findings stem from retrospective assessments, conducted through questionnaires/parental interviews (involving large databases such as InterRett or the Australian Rett syndrome database), retrospective trawls through pre-diagnostic medical records[44,45] or retrospective video analysis.[9–11,13,15–21,37] The prospective approach presented here is entirely novel to the field of studying RTT precursors. From the literature in studying suboptimal development, or development of children with genetic disorders, we know that parents appear to be able to give an accurate estimation of what is happening not only in relation to their child's general development when asked at the time of 'happening events',[46–49] but also in relation to more specific aspects, such as speech-language development.[50,51] The DNBC study offered us the opportunity to develop a new approach for investigating RTT through collecting quasi prospective and concurrent data on early development.

The original idea underpinning this approach was to use prospectively collected data on children later diagnosed with RTT, enabling access to observations made at the time of "events happening" (and not knowing the later diagnosis of the child) rather than reconstructing events from the past, which could introduce bias. In reality, unfortunately, we had to contend with both concurrent and retrospective data due to (a) the study design, for example, parents were asked during the 18 month interview to provide the age at which their child could sit and/or walk alone, which are milestones usually achieved at a younger age; and (b) the fact that not all parents could be reached in the intended two-week timeframe. Thus, the problems associated with reliance on retrospective analysis could not be avoided completely (quasi prospective approach). Moreover, as a few girls were already diagnosed with RTT by the age of 18 months, this may have influenced the way in which the developmental questions were answered. Furthermore, the results must be treated with some caution as

the RTT sample in this study was very small in comparison with the main cohort. This will be, by definition, the case for any study of a rare disorder such as RTT and can only be overcome as more studies of this sort are undertaken, ensuring a critical mass of data can be reached. Finally, it should be noted as a further limitation that neither the data acquisition nor the interviews were designed specifically to ask for peculiarities in early development. For further cohort studies aiming to pinpoint specific neurodevelopmental disorders specifically designed questions to potentially detect peculiarities in early development and different time points of assessment should be considered. Early detection is the key to learn more about early development in a prospective rather than retrospective manner in the future and will certainly lead to earlier intervention, be it general symptomatic or targeted.

Conclusion

Even though the mean age of diagnosis has decreased to around 2 1/2 years for classic RTT and a little more than a year later for atypical RTT,[52] we still have some way to go in delivering a comprehensive description of the early development of girls later diagnosed with RTT. In our sample the mean age of diagnosis was even some six months earlier than the recently reported average diagnostic age.[52] We cannot yet say with absolute certainty whether the absence of certain behaviors is within the range of normal development, or is shared by all those with certain other developmental disorders, or by those with a severe intellectual disability regardless of cause, or whether they are unique to a certain disorder such as RTT,[10] (p. S7). The quasi prospective methodology of the current study is promising, yet in order to add substantially to what we already know about RTT, specific questions addressed to parents need to be designed. As this involves much work when conducting large cohort studies, it may be more realistic to consider a set of indicators which could potentially point to a number of developmental disorders. Professionals need to be aware that parents are valuable informants about their child's concurrent behaviors and should take their thoughts and concerns into account.[23,44] With early alerts, however, come professional and ethical/moral responsibilities, a duty to be able to offer early help and support to families.[10,53] Early detection also requires early intervention and this should not be forgotten.

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Declaration of interest

The authors report no declarations of interest.

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